Tautomerism in Hydroxynaphthaldehyde Anils and Azo Analogues: a Combined Experimental and Computational Study

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The enol imine ⇄ enaminone tautomerization constants, K_T, and thermodynamic parameters, ΔH_T and ΔS_T, of 1-hydroxy-2-naphthaldehyde Schiff bases are determined by UV/vis spectroscopy. Polar solvents shift the equilibrium toward the quinone form (for the unsubstituted derivative **1c**, $K_T = 0.20$ (cyclohexane) and $K_T = 1.49$ (ethanol)). Both donor (MeO, NMe_2) and acceptor (CN, NO_2) substituents lead to a decreased K_T independent of solvent polarity. In apolar solvents, for all derivatives **1a**−**1e**, the enol imine ⇄ enaminone equilibria are endergonic but exothermic. Linear solvation energy relationships allow extrapolation of ΔG_T to the gas phase. Density functional theory calculations (B3LYP/6-311+G**) yield good agreement with these extrapolated ΔG_T values. Solvent effects on **1c** are also successfully reproduced by the calculations. Geometric (O···N distance) and energetic criteria (conformer energy differences, homodesmotic reactions) establish the importance of intramolecular hydrogen bonding for the tautomerism of these compounds. The results obtained for **1a**−**1e** are compared with tautomeric properties of the isomeric naphthaldehyde anils **2**−**4**, the monocyclic analogues **5** and **6**, the corresponding azo derivatives **7**−**9**, and the *N*-alkyl derivative **10**.

Introduction

Intramolecular proton transfer in the ground and/or excited state of Schiff bases has important consequences on their electronic structure which can be exploited for their thermochromic and/or photochromic behavior,[1,2] the design of molecular electronic devices,[3] and their suitability as agents in photodynamic cancer therapy.[4] Furthermore, intramolecular hydrogen bonding in 1,3-diketones, β-enaminones or ketohydrazones,[5−7] and related heterodienes[8] is of fundamental importance in the theory of hydrogen bonding.[9−11]

In view of this general interest in the prototropic properties (enol imine (phenol, **A**) ⇄ enaminone (keto amine, quinone, **H**) tautomerism) of hydroxy naphthaldehydes, Schiff bases, or salicylidene anils, as well as the long-known azo ⇄ hydrazo tautomerism of hydroxy azo compounds,[12] numerous experimental investigations on such compounds (X-ray crystallography, UV/vis, fluorescence, and NMR spectroscopy, as well as combinations thereof) have been performed; as a complement to these experiments, a variety of computational chemistry methods also has been applied.[1−8,13−29] Unfortunately, estimating tautomeric equilibria by computational methods can be fiendishly difficult,[30] necessitating calibration of calculated tautomerization energies with the aid of experimental results. However, so far, it has been difficult to obtain reliable quantitative experimental data on these equilibria.[18a,b] In the following, we present a combined experimental (chemometric analysis of UV−Vis spectra[18a,b]) and computational investigation of the tautomeric equilibria of substituted 1-hydroxy-2-naphthaldehyde anils **1** (Scheme 1). Special emphasis will be put not only on the effect of substituents (donor vs acceptor) on the tautomerization constant, K_T = [quinone]/[phenol], but also on the influence of solvation, the importance of intramolecular hydrogen bonding, positional isomerism, and the effect of the additional benzene ring in naphthyl derivatives as opposed to salicylidene anils or hydroxy azobenzenes. Thus, to put the results obtained for **1** into a broader context, comparison will be made with the isomeric anils of 2-hydroxy-1-naphthaldehyde, 3-hydroxy-2-naphthaldehyde, and 4-hydroxy-1-naphthaldehyde **2**−**4**, salicylidene anil **5**, and 4-phenyliminomethylphenol **6**. In addition, phenylazonaphthols **7**−**9** are also included (Scheme 1). The effect of the *N*-aryl group on K_T is estimated by comparison with the alkyl derivative **10**.

Results

Experimental Results. In this section, first, tautomerization constants K_T = [quinone]/[phenol] for compounds **1a**−**e** will be presented and compared to the related structures **2**−**10** (Scheme 1). Second, a more detailed description of solvent effects on K_T of **1c**, as well as their treatment by linear solvation energy relationships, will be given. Finally, thermodynamic parameters of the imino phenol ⇄ enaminone (azo ⇄ hydrazo) tautomeric equilibria will be presented.

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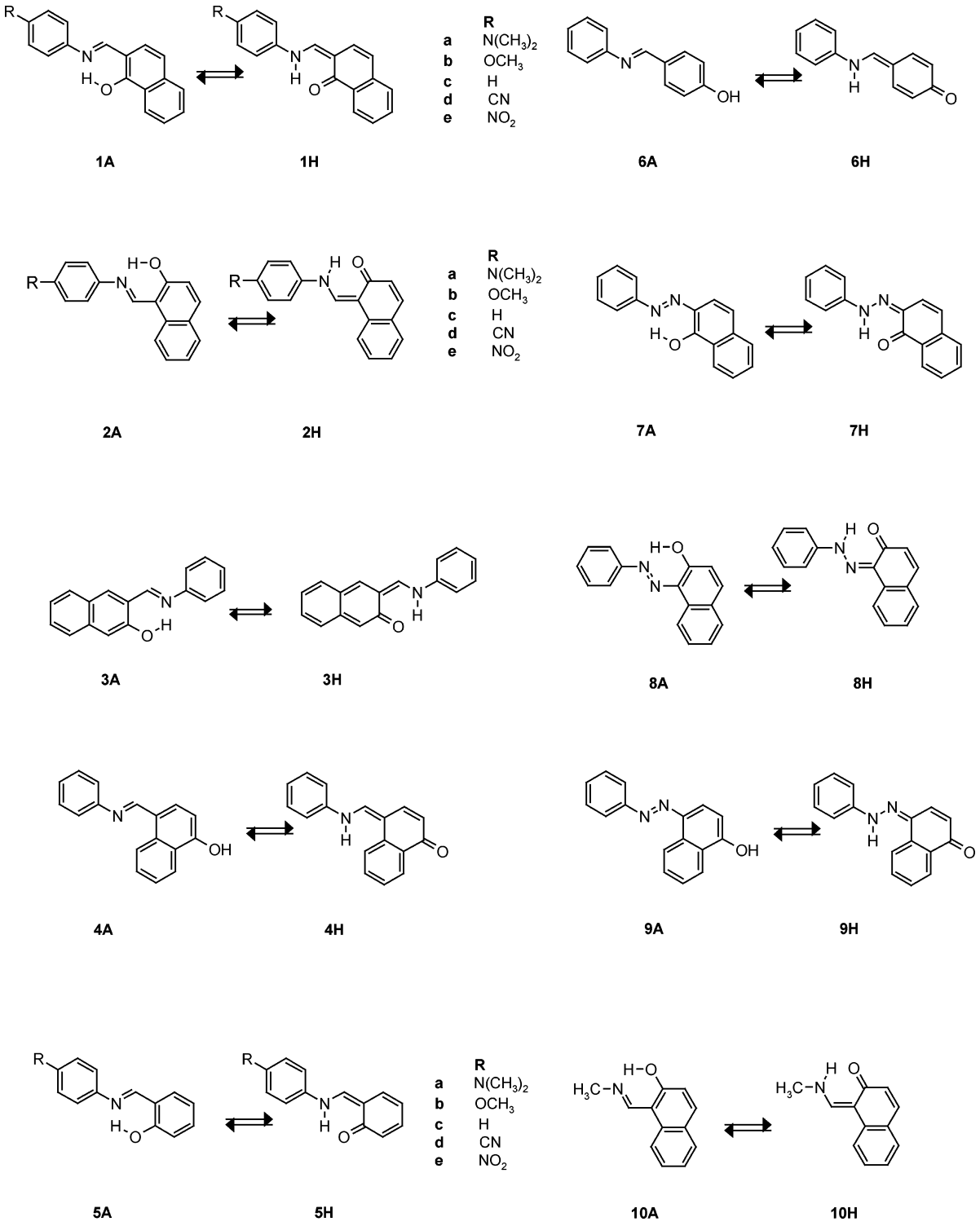
SCHEME 1: Structures of the Investigated Compounds



1. Tautomerization Constants. Observed (or, estimated, see Experimental section) UV/vis absorption bands of the individual tautomeric forms (imino phenol **A** and enaminone **H**) for Schiff bases **1a**−**e**, as well as tautomerization constants, K_T = [quinone]/[phenol], derived therefrom via chemometric analysis of the spectral data, are summarized in Table 1. K_T values for all five derivatives were determined in apolar (cyclohexane), polar aprotic (acetonitrile), and polar protic (ethanol) solvents. Both donor (**1a**, **1b**) and acceptor substituents (**1d**, **1e**) cause bathochromic shifts of the longest wavelength absorption bands of either tautomeric form. A similar dependence of the UV/vis spectra on substituents has previously also been found for the isomeric 2-hydroxy-1-naphthaldehyde anils **2a**−**e**.[27a] Time dependent density functional calculations (TD-B3LYP/6-31+G**) are in line with these experimental findings (Table 1). Whereas band positions of the UV/vis spectra are essentially independent of solvent polarity, tautomerization constants of **1a**−**e** show a clear increase in the order cyclohexane < acetonitrile < ethanol, in line with the expected higher polarity of the quinone tautomer and, thus, preferential stabilization by polar solvents. The dependence of the overall shape of the UV/vis spectra of compound **1c** on solvent polarity is shown in Figure 1.

Thereby, the different tautomer content **1cA** vs **1cH** clearly can be seen. Also, the negligible solvent shift of the various

TABLE 1: UV/Vis Data, Enol Imine ⇄ Keto-Amine Equilibrium Constants K_T, Experimental (in parentheses) and Calculated ΔG_T Values of Compounds 1a−1e in Various Solvents

		A form		H form		cyclohexane		acetonitrile		ethanol	
compd	R	λ_{max}/nm[a]	λ_{max}/nm[b]	λ_{max}/nm[a]	λ_{max}/nm[b]	$K_T(\Delta G_{exp})$	ΔG_{calc}[c]	$K_T(\Delta G_{exp})$	ΔG_{calc}[c]	$K_T(\Delta G_{exp})$	ΔG_{calc}[c]
1a	$N(CH_3)_2$	406 (390, 410, 432)	387	477 (452, 481, 507)	400	0.11 ± 0.02	−0.97	0.88 ± 0.09	−2.07	7.85[d]	−3.70
						(1.31 ± 0.10)	(−1.78)	(0.08 ± 0.06)	(−3.71)	(−1.22)	(−3.61)
1b	OCH_3	387	359	457 (438, 460, 485)	392	0.10 ± 0.01	−0.75	0.63 ± 0.03	−1.64	1.21 ± 0.05	−2.64
						(1.36 ± 0.06)	(−1.64)	(0.27 ± 0.03)	(−3.58)	(−0.11 ± 0.02)	(−3.56)
1c	H	383	354	454 (433, 458, 482)	397	0.20 ± 0.01	−1.14	1.24 ± 0.06	−2.07	1.49 ± 0.08	−2.42
						(0.95 ± 0.03)	(−1.95)	(−0.13 ± 0.03)	(−3.85)	(−0.24 ± 0.03)	(−3.78)
1d	CN	397	373	463 (448, 467, 492)	417	0.07 ± 0.01	−1.02	0.57 ± 0.05	−1.76	0.64 ± 0.07	−2.09
						(1.57 ± 0.08)	(−1.84)	(0.33 ± 0.05)	(−3.81)	(0.26 ± 0.06)	(−3.72)
1e	NO_2	403	407	475 (461, 478, 504)	445	0.06 ± 0.01	−1.79	0.56 ± 0.08	−2.44	0.60 ± 0.09	−2.73
						(1.66 ± 0.09)	(−2.65)	(0.34 ± 0.08)	(−4.69)	(0.30 ± 0.08)	(−4.54)

[a] Spectral characteristics of the individual tautomeric forms (sub-bands are given in parentheses) estimated according to ref 18a,b. The values in all solvents are practically the same (see Figure 1). [b] Calculated values (TD-B3LYP/6-31+G**). [c] PCM-B3LYP/6-311+G**//HF-6-31G* + p(H) results (PB-SCRF-B3LYP/6-311+G** ΔG values are given in parentheses). [d] Due to strongly overlapping bands, this value is only approximate.

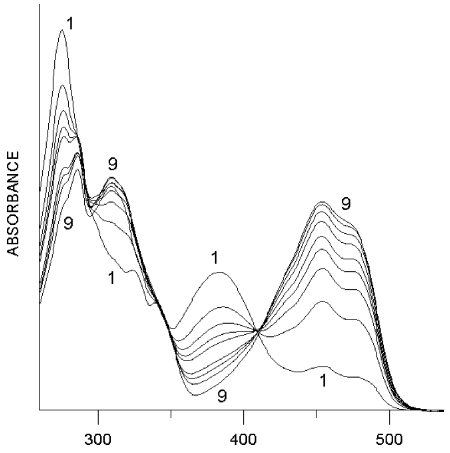


Figure 1. Absorption spectra of **1c** in 1, CH; 2, 80/20 CH/EtOH; 3, 60/40 CH/EtOH; 4, 40/60 CH/EtOH; 5, 20/80 CH/EtOH; 6, EtOH; 7, 80/20 EtOH/Water; 8, 60/40 EtOH/Water; and 9, 40/60 EtOH/Water.

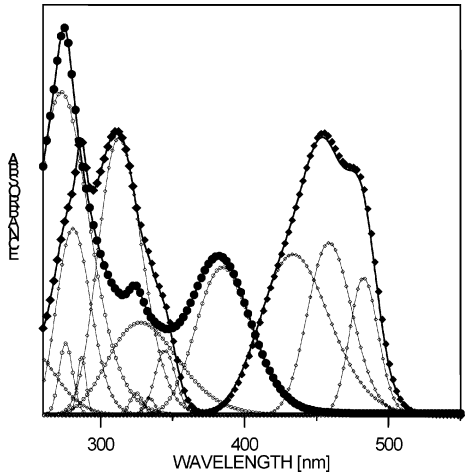


Figure 2. Individual spectra of **A** (filled circles) and **H** (filled diamonds) forms of **1c** along with the decomposed individual bands (empty characters) obtained through chemometric data processing of the data from Figure 1.

band maxima of the individual tautomers is evident. As an example, the decomposition of the UV/vis spectrum of the **1cA** ⇄ **1cH** tautomeric mixture into individual bands according to the procedure described in detail previously[18a,b] is given in Figure 2.

Except for K_T of **1a** in ethanol, which because of strongly overlapping bands is only approximate, substituents—especially acceptors (CN, NO_2)—decrease the amount of enaminone content in the equilibrium mixture. Thus, for all derivatives, the imino enol form predominates in cyclohexane; in acetonitrile, the enaminone form of the unsubstituted derivative **1c** and, in ethanol also, of the donor (MeO, NMe_2) substituted derivatives is prevalent. The effect of the substituent on K_T is, however, quite small as also found in the case of 2-hydroxy-1-naphthaldehyde Schiff bases **2**[27a] and salicylidene anils **5**.[26a] In these latter two derivatives, contrary to **1**, donor substituents apparently stabilize the quinone tautomer, at least in polar protic media (EtOH, MeOH). Positional isomerism, i.e., **1** vs **2**, has only little influence on K_T: for R = H, K_T values obtained in different solvents are in the range 0.20−1.25 in **1** (Table S1, Supporting Information), those in **2** are in the range 0.1−1.1.[27a] In complete contrast, anils of 3-hydroxy-2-naphthaldehyde **3** have been reported to exist exclusively as the imino enol tautomer.[14c]

Proton transfer from the imino enol tautomer to the keto amine form is accompanied by a benzenoid−quinonoid structural change with a concomitant loss of aromaticity. In **1** and **2**, this change is restricted to only one ring of the naphthalene moiety, whereas in **3**, both are involved (see structures in Scheme 1), making **3H** considerably less stable than **3A**. Unlike hydroxyazobenzenes or salicylidene anils, which mainly or almost exclusively exist as azo (imino enol) tautomers,[24a] there is a significant or even predominant quinone content in the naphthol derivatives. Only recently has it been possible by the more sensitive fluorescence excitation spectroscopy to determine tautomerization constants in **5**,[26a] and they were found to be at least an order of magnitude lower than those in **1** or **2**. The same argument as above—complete loss of aromaticity rather than only for one ring—has been put forward to explain this difference.[15a,b] Arylazonaphthols are slightly more prone to form the hydrazo tautomers (K_T = 1.5−2.5 for 2-phenylazo-1-naphthol **7**[27b] and 0.5−1.6 for 1-phenylazo-2-naphthol **8**[27c]). Considerably larger K_T values (K_T = 2−9) have been reported for the *N*-alkyl derivative **10**.[31]

2. Linear Solvation Energy Relationships. Although correlation of K_T with solvent polarity as described by its relative permittivity, D (Table S1), is modest (r^2 = 0.73), polar solvents

TABLE 2: Thermodynamic Parameters for the Enol Imine ⇄ Keto-amine Equilibrium of Compounds 1, 2, 7−9 in Methylcyclohexane/Toluene (Results for Ethanol Are Given in Parentheses)

compd	ΔH_T [kcal mol^{-1}]	ΔS_T [cal mol^{-1}K^{-1}]	compd	ΔH_T [kcal mol^{-1}]	ΔS_T [cal mol^{-1}K^{-1}]
1a	−0.535 ± 0.053	−6.44 ± 0.26	**2**[a]	−0.198 ± 0.013 (−0.598 ± 0.038)	−5.43 ± 0.08 (−2.18 ± 0.25)
1b	−0.442 ± 0.055	−6.36 ± 0.28	**7**[a]	−0.584 ± 0.021 (−0.384 ± 0.034)	−1.19 ± 0.09 (−0.31 ± 0.17)
1c[a]	−0.481 ± 0.067 (−0.664 ± 0.043)	−4.76 ± 0.32 (−1.43 ± 0.16)	**8**[a]	−0.463 ± 0.004 (−0.089 ± 0.012)	−2.95 ± 0.02 (−0.98 ± 0.05)
1d	−0.553 ± 0.026	−7.36 ± 0.12	**9**[a]	−0.115 ± 0.014 (0.526 ± 0.033)	−4.60 ± 0.01 (−1.65 ± 0.11)
1e	−0.836 ± 0.043	−8.62 ± 0.21			

[a] Data from ref 18d.

clearly increase the amount of the enaminone tautomer. A similar result is also found for the imino enol ⇄ keto amine tautomerism of isomeric 2-hydroxy-1-naphthaldehyde anils **2**[27a] ($r^2 = 0.75$) and the azo ⇄ hydrazo tautomerism of 1-phenylazo-2-naphthols **8**[27c] ($r^2 = 0.81$). In striking contrast, both 2-phenylazo-1-naphthol[27b] and 4-phenylazo-1-naphthol[27d] lack any clear correlation of K_T with solvent polarity (relative permittivity D, $r^2 = 0.05$ and $r^2 = 0.21$, respectively).

A more satisfactory description of solvent effects on K_T can be achieved by using the solvatochromic parameters α (proton donor ability of the solvent), β (proton acceptor ability of the solvent), and π^* (polarity−polarizability) in linear solvation free energy relationships (eq 1, Table S2).[32]

$$\log K_T = c + s\pi^* + a\alpha + b\beta \qquad (1)$$

Anils **1** and **2** show significant terms in π^* and α but not in β. The absence of a β term can be attributed[32b] to strong intramolecular hydrogen bonding (resonance-assisted H-bonds[5]). As evidenced by the value of the coefficient b, this intramolecular hydrogen bonding is weaker in azo compounds **7** and **8** and can be broken by proton-accepting solvents. The negative sign indicates stronger hydrogen bonding of the solvent to the azo than the hydrazo tautomer. 4-Phenylazonaphthol **9**, where no intramolecular hydrogen bonding is possible, shows the most negative coefficient of the β term. No such comparison can be made in the case of Schiff bases **1**, **2**, and **4** since, because of the frequently observed[17d] extensive dimerization/oligomerization, K_T for **4** could not be determined. All six compounds (Table S2) show positive α and π^* terms, meaning greater stabilization of the quinone tautomer. The effect of α can be attributed to stronger hydrogen bonding between the solvent and the carbonyl oxygen than with the phenolic oxygen and/or aza-nitrogen of the bridge, while the sign of π^* indicates a greater polarity of the enaminone (hydrazo) tautomers.

3. Thermodynamic Parameters. Thermodynamic parameters of the enol imine ⇄ enaminone tautomeric equilibria for **1a**−**1e** obtained from the temperature dependence of K_T in methylcyclohexane/toluene are summarized in Table 2. For comparison purposes, the corresponding data for **2** and **7**−**9** determined previously[18d] are also listed there. In apolar solvents, e.g., methylcyclohexane/toluene, for all compounds, formation of the quinonoid tautomer is exothermic ($\Delta H_T < 0$). It is entropy which makes the imino enol ⇄ enaminone (azo ⇄ hydrazo) tautomeric equilibria endergonic ($\Delta G_T > 0$) in apolar solvents for all systems but 2-phenylazo-1-naphthol **7**. An important entropy contribution has also been found for salicylidene anils **5**.[26a] However, the above-mentioned complete loss of aromaticity makes imino enol ⇄ enaminone tautomerization of **5** not only endergonic but also endothermic ($\Delta H_T > 0$). Hydroxynaphthaldehyde Schiff bases **1** and **2** differ also in another respect

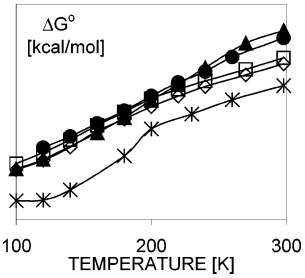


Figure 3. ΔG_T of compounds **1a**−**1e** as a function of the temperature (**1a** -◇-; **1b** -□-; **1c** -*-; **1d** -●-; **1e** -▲-).

from the monocyclic analogues **5**: both donor and acceptor substituents decrease ΔH_T in the case of **1** and **2**, i.e., favor the quinonoid structure; in the case of compound **5**, only donor substituents decrease ΔH_T, whereas acceptors lead to an increase in ΔH_T. In both naphthyl and phenyl derivatives, the entropic contribution is larger for compounds substituted by more polar groups. The influence of solvent polarity (methylcyclohexane/toluene vs ethanol) on ΔH_T is different for naphthaldehyde Schiff bases compared to the corresponding arylazonaphthols **7**−**9**: ΔH_T values are more negative in ethanol than in methylcyclohexane/toluene for **1** and **2** and less negative, or even positive (**9**), in the case of the azo compounds.

Finally, the temperature dependence of ΔG_T (in methylcyclohexane/toluene) for substituted derivatives of **1** is fundamentally different from that of the unsubstituted derivatives **1c**, **2**, **7**, **8**, and **9**: the latter all show two distinct regions (300−200 and 200−120 K, respectively), yielding two sets of thermodynamic parameters ΔH_T and ΔG_T; in the case of the substituted Schiff bases **1a**, **b**, **d**, and **e**, no such behavior is found. The temperature dependence of ΔG_T in the range 100−300 K of compounds **1a**−**e** (methylcyclohexane/toluene) is shown in Figure 3. For **2** and **7**−**9**, previously ΔG_T vs T curves similar in shape to that of **1c** (and different to the substituted derivatives **1a**, **b**, **d**, and **e**) have been obtained.[18d]

Computational Results. In the following, the intrinsic (gas phase) stability of the individual tautomeric forms will be treated by quantum chemical (ab initio HF and MP2, as well as density functional theory (B3LYP)) methods. First, the reliability of the computational procedures used will be assessed. In the second section, various solvation models will be applied to estimate the effect of solvent polarity on the imino phenol ⇄ enaminone (azo ⇄ hydrazo) tautomerism. Finally, several calculated structural and energetic parameters will be used to assess the influence of intramolecular hydrogen bonding on K_T.

1. Intrinsic Tautomer Stability. First, the reliability of different computational procedures (HF, B3LYP, MP2) and basis sets with respect to the calculation of tautomerization energies, will be addressed. Since the tautomerization enthalpy,

TABLE 3: Calculated Relative Enthalpies, ΔH[a], for Different Conformations of the Enol Imine and Enaminone Tautomer and Transition State for Proton Transfer of Compound 1c

1c	I[b]	II[c]	III[d]	IV[e]
A1	0.0	0.0	0.0	0.0
A2	15.0	14.4	15.5	14.9
A3	10.5	9.9	11.4	10.7
A4	10.7	9.5	11.1	10.5
H1	−0.3	4.6	−0.1	5.5
H2	7.2	12.6	8.3	14.6
TS	−0.4	1.6	1.2	3.2

[a] In kcal mol^{-1}; for structures of conformers, see Scheme 2. [b] B3LYP/6-311+G**//HF/6-31G* + p(H). [c] MP2/6-311+G**//HF/6-31G* + p(H). [d] B3LYP/6-311+G**//B3LYP/6-31+G**. [e] MP2/6-311+G**//B3LYP/6-31+G**.

ΔH_T, of **1c** is remarkably insensitive to the solvent used (Table 2), it should be a good approximation to the corresponding calculated gas-phase value. Consequently, we use this datum to estimate the reliability of our computational procedures. Extensive testing (for total energies, see Tables S3−S5 and for tautomerization energies, see Table S6 of the Supporting Information) indicates that (i) except at the lowest levels, the basis set and procedure (HF, B3LYP) used for geometry optimization are of little relevance; (ii) with B3LYP, a slightly greater stability of the quinone (enaminone) tautomer is obtained, whereas HF, and even more so, MP2 predict a greater stability of the phenol (enol imine) form of **1c** (Table 3).

Interestingly, for the bis-azo dye Sudan III not only B3LYP but also MP2 calculations predict the hydrazo (quinone) tautomer to be more stable,[25a] indicating that care has to be taken in generalizations, even for closely related systems. As a reasonable tradeoff between computational costs and reliability of tautomerization energies, we suggest using B3LYP/6-311+G** single point calculations at HF/6-31G* + p(H) geometries (here, p(H) indicates a basis set with p-type polarization functions ($\alpha = 1.1$) added only to the moveable hydrogen). However, energies are only one aspect; intramolecular hydrogen bonding (resonance assisted hydrogen bonding[5]) is expected to play a crucial role for the tautomerization equilibria as demonstrated for simple enaminones[7] or nitroethylenes.[8] Apparently, for a correct description of the geometry of such systems, electron correlation has to be taken into account by MP2 or DFT methods.[33] A comparison of calculated pertinent structural parameters for the intramolecular hydrogen bond with averaged X-ray data from a CSD search[34] is shown in Table 4. Clearly, B3LYP geometries are generally superior to those obtained by Hartree−Fock calculations, whereas B3LYP energies are surprisingly insensitive to the geometry used (Table 3).[35] Most important, B3LYP/6-311+G** results ($\Delta H_T = -0.1$ kcal mol^{-1} (B3LYP/6-31+G** geometry) and $\Delta H_T = -0.3$ kcal mol^{-1} (HF/6-31G* + p(H) geometry), Table 3) are in good agreement with the experimental tautomerization enthalpy for **1c** determined in methylcyclohexane/toluene ($\Delta H_T = -0.5$ kcal mol^{-1}, Table 2).

Having established an appropriate computational procedure, we now turn to the substituent effect on the tautomeric equilibria of 1-hydroxy-2-naphthaldehyde Schiff bases **1a**−**1e**. Calculated tautomerization enthalpies for **1**−**9** are collected in Table 5 and Table S7 of the Supporting Information. Generally, the stability of the enaminone tautomer is underestimated (calculated ΔH_T values less negative than experimental ones). The calculated influence of substituents on K_T of 1-hydroxy-2-naphthaldehyde Schiff bases, however, is in excellent agreement with the experimental results ($r^2 = 0.966$ (HF/6-31G* + p(H) geometry) and $r^2 = 0.997$ (B3LYP/6-31+G** geometry)) provided, for **1c**, the low-temperature value of ΔH_T is used.

TABLE 4: Comparison of Calculated Structural Data of Compound 1c Pertinent to Intramolecular Hydrogen Bonding with Averaged X-Ray Data[a]

		I[b]	II[c]	III[d]
1c-A1	R(C1−O9)	1.325	1.338	1.348
	R(C1−C2)	1.380	1.409	1.405
	R(C2−C11)	1.461	1.446	1.447
	R(C11−N12)	1.264	1.297	1.286
	R(O9−H10)	0.958	1.006	0.937
	R(N12−H10)	1.853	1.682	1.764
	R(O9−N12)	2.684	2.593	2.592
	<(O9−H10−N12)	143.6	148.5	146.3
	Δ[e]	0.041	0.025	
1c-H1	R(C1−O9)	1.220	1.260	1.295
	R(C1−C2)	1.461	1.463	1.428
	R(C2−C11)	1.368	1.393	1.421
	R(C11−N12)	1.331	1.339	1.304
	R(O9−H10)	1.912	1.738	1.740
	R(N12−H10)	1.002	1.036	0.939
	R(O9−N12)	2.676	2.606	2.558
	<(O9−H10−N12)	130.8	138.5	144.2
	Δ[e]	0.077	0.040	

[a] Distances in Å, angles in degrees. [b] HF/6-31G* + p(H). [c] B3LYP/6-31+G**. [d] X-ray. [e] Mean unsigned error.

TABLE 5: Calculated Gas Phase Tautomerization Enthalpies for 1−9[a]

	I[b]	II[c]		I[b]	II[c]
1a	0.06	0.19	**5a**	5.38	4.43
1b	0.15	0.25	**5b**	5.60	4.67
1c	−0.33	−0.12	**5c**	5.27	4.50
1d	−0.02	0.16	**5d**	5.85	4.98
1e	−0.15	0.00	**5e**	5.78	4.94
2	0.60	0.81	**6**	8.64	7.98
3	9.55	-[d]	**7**	−2.28	−1.90
4	1.25	1.93	**8**	−1.57	−0.99
			9	0.62	−0.52

[a] In kcal mol^{-1}. [b] B3LYP/6-311+G**//HF/6-31G* + p(H). [c] B3LYP/6-311+G**//B3LYP/6-31+G**. [d] With B3LYP/6-31+G**, no stable minimum for the quinone tautomer could be found.

TABLE 6: Estimated[a] (ΔG_T^{gas}) and Calculated Gas Phase Tautomerization Gibbs Free Energies[b]

	ΔG_T^{gas}	I[c]	II[d]
1c	1.961	−0.76	−0.87
2c	2.859	0.09	0.12
7	−0.027	−2.33	−1.94
8	0.585	−1.26	−1.06
9	3.063	0.64	−0.60

[a] From linear solvation energy relationships. [b] In kcal mol^{-1}. [c] B3LYP/6-311+G**//HF/6-31G* + p(H). [d] B3LYP/6-311+G**//B3LYP/6-31+G**.

Gas-phase tautomerization free energies, ΔG_T, can be extrapolated with the aid of the linear solvation energy relationships described above (eq 1, $\pi^* = -1.23$ in vacuo[32c]) (Table 6). As expected, in the gas phase, the equilibrium is shifted toward the less polar enol imine (azo) tautomer ($\Delta G_T = 1-3$ kcal mol^{-1}); only for 2-phenylazo-1-naphthol **7**, even in the gas phase, the hydrazo form should slightly be predominant. Calculated ΔG_T values generally are too low, but the trend is in good to excellent (HF/6-31G* + p(H) geometry, $r^2 = 0.971$; $\Delta G_T^{gas} = 1.14\Delta G_T^{calc} + 2.52$) agreement with experiment.

For anil **4**, which until now has eluded experimental determination of K_T, the above regression equation yields $K_T \approx 0.004$. Completely in line with experimental data,[24a,26a] the calculations result in considerably larger ΔG_T values, i.e., greater stability

TABLE 7: Solvent Effect on Tautomerization Gibbs Free Energies of Compound 1c

solvent	ΔG_T^{exp}	I[a]	II[b]	III[c]	IV[d]	V[e]
H_2O	−0.67	−4.78	−2.50	−4.54	−4.74	−4.29
DMSO	0.11	−3.85	−2.03	−4.06	−2.81	−3.50
acetonitrile	−0.13	−3.85	−2.07	−4.07	−2.76	−3.52
methanol	−0.09	−3.94	−2.45	−3.98	−4.55	−3.70
ethanol	−0.24	−3.78	−2.42	−3.97	−4.47	−3.48
acetone	0.47	−3.72	−2.01	−3.89	−2.68	−3.38
CH_2Cl_2	0.25	−3.35	−1.81	−3.52	−2.45	−3.13
toluene	0.71	−2.17	−1.34	−2.18	−1.92	−1.94
cyclohexane	0.95	−1.95	−1.14	−2.01	−1.66	−1.70
Et_2O	0.84	−2.92	−1.83	−3.00	−2.75	−2.51
gas phase	1.96	−0.76	−0.76	−0.87	−0.87	−0.87

[a] PB-SCRF/B3LYP/6-311+G**//HF/6-31G* + p(H). [b] PCM/B3LYP/6-311+G**//HF/6-31G* + p(H). [c] PB-SCRF/B3LYP/6-311+G**//B3LYP/6-31+G**. [d] PCM/B3LYP/6-311+G**//B3LYP/6-31+G**. [e] IEF-PCM/B3LYP/6-31+G**//IEF-PCM/B3LYP/6-31+G**.

of the aromatic phenol tautomer, for salicylidene anil **5** and the corresponding para isomer **6**.

2. Solvent Effects on Calculated Tautomerization Energies. Solvent polarity profoundly affects the imino enol ⇄ enaminone (azo ⇄ hydrazo tautomerism) in Schiff bases (azo phenols) by stabilizing the more polar quinone forms, although frequently no clear-cut relation between K_T and solvent polarity (relative permittivity, D) could be established.[27] To estimate solvent effects on calculated tautomerization energies, both bulk solvation models,[7a,27a] as well as explicit solvent molecules, have been used.[26a,27a,e,f] In the following, several variants[36] of the polarizable continuum (PCM,[36b,c] IEF−PCM,[36d] CPCM,[36e] SCIPCM[36f]) and the Poisson−Boltzmann SCRF (PB-SCRF)[37] solvation model will first be applied to the tautomeric equilibrium of **1c**. In addition to single point calculations on gas-phase geometries, the effect of optimization in solvent (IEF-PCM/B3LYP/6-31+G**) on calculated K_T values will also be addressed (Tables 7, S8, and S9).

We find that even for apolar solvents, e.g., cyclohexane, bulk solvation models greatly overestimate the stabilization by solvent of the enaminone tautomer yielding considerably too negative ΔG_T values. In contrast, the general trend exerted by solvents of quite different polarity and protic/aprotic nature can be described very successfully by these models (Table 7).

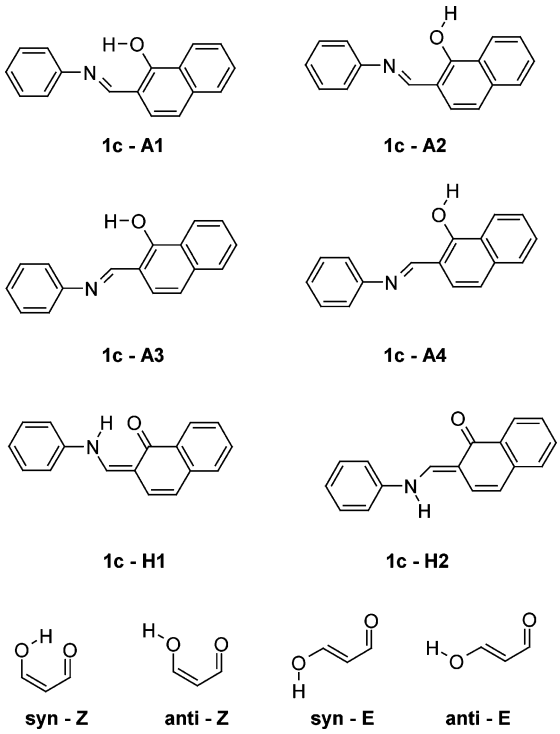
Optimization in solvent (IEF-PCM, B3LYP/6-31+G**) does not further improve the results. Previously, a detailed investigation on the solvent effect (aqueous solution) on tautomer and conformer stabilities, geometries, and strength of intramolecular hydrogen bonds in the prototype β-aminoacrolein[7a] also had indicated that full optimization in solvent is not really necessary. Instead, inclusion of explicit solvent molecules, even at a moderate level of theory, appears more promising.[26a,27a] In contrast to the substituted salicylidene anils **5a**−**e** (Table S8), for the analogous Schiff bases of the isomeric hydroxy naphthaldehydes, **1a**−**e** and **2a**−**e**, neither the polarizable continuum nor the PB-SCRF model correctly describes the solvent effects, even in cyclohexane (!), on K_T values (Table S9 of the Supporting Information).

3. Effect of Intramolecular Hydrogen Bonding. Intramolecular O−H···N and O···H−N hydrogen bonding is a prominent feature of hydroxy azobenzenes and the analogous Schiff bases, comparable to, if not even more important than, the homonuclear O−H···O bond in enols of β-dicarbonyl compounds.[5,6,9,14d,20,21,38] Computationally, the importance of intramolecular hydrogen bonding on the position of the tautomeric equilibria of the parent β-aminoacrolein and in nitroethylenes has been studied in detail.[7,8] To address the strength of intramolecular hydrogen bonds, several criteria, e.g., geometric, energetic and topological, have been suggested,[5a,b,7c,8,10,25e,29,39] with each one having some advantages or shortcomings.[10a] Several of these criteria (N···O distance, conformational energy differences, barrier to proton transfer, homodesmotic reactions and NBO analysis) will be described in the following.

3.1. Geometric Criteria for Hydrogen Bonding. Among the geometric criteria, the N···O distance apparently gives a good indication of H-bond strengths, whereas the N−H lengthening due to strong (resonance-assisted) H-bond formation is small or even irrelevant.[5b] We find that the differences between the calculated (B3LYP/6-31+G** geometry) N···O distances (Table S10) of the enol imine and enaminone tautomers, respectively, of compounds **1a**−**e**, **2c**, **5a**−**e**, **7**, **8**, and **10** correlate quite nicely with the corresponding K_T values ($r^2 = 0.979$). It is also evident from these data that the stronger hydrogen bond (shorter N···O distance) is associated with the less stable tautomer.[5a,b,7,8] Interestingly, despite less reliable absolute structural parameters, a similarly good correlation is also obtained with HF/6-31G* + p(H) geometries ($r^2 = 0.981$). For the aliphatic analogue **10** of the 2-hydroxy-1-naphthaldehyde Schiff base **2**, the calculated (HF/6-31G* + p(H) geometries) N···O distances indicates stronger intramolecular hydrogen bonding than in case of compound **2**. The difference, however, is comparable to the anils and, thus, this derivative fits quite well to the r(N···O) vs log K_T correlation (log $K_T(CHCl_3) = 0.40$,[31] $r^2 = 0.980$). The importance of intramolecular hydrogen bonding on K_T is further evidenced by r(N···O) calculated for **1c** in different solvents (B3LYP/6-31+G**, IEF-PCM, $r^2 = 0.859$). For the solvent effect on vibrational frequencies,[6c] we find for **1c** a decrease for ν (O−H) and an increase for ν (N−H), respectively, with increasing solvent polarity (Table S11). Since both ν (O−H) and ν (N−H) are linearly correlated with the respective N···O distance and, thus, inversely with the strength of the respective intramolecular H-bond, this behavior indicates strengthening of the O−H···N and weakening of the N−H···O H-bond by polar solvents with a concomitant shift of the tautomeric equilibrium toward the enaminone form. This exactly is observed experimentally.

3.2. Conformer Energies. Despite some shortcomings,[7,8] the difference between energies of conformers with and without intramolecular hydrogen bonds (Scheme 2) or rotational barriers has widely been used as an energetic criterion for H-bond strengths.[5a,b,7,8] In the case of the parent substituted ethylenes,[7,8] by judiciously choosing the respective conformations (*E/Z* and syn/anti, Scheme 2), at least some of the inherent drawbacks can be accounted for; in the case of the naphthaldehyde Schiff bases or azo derivatives, not all *E/Z* isomers exist. Furthermore, severe steric hindrance can also cause strong repulsive nonbonded interactions in syn/anti isomers, making H-bond energies evaluated in this way largely meaningless.[5b] Especially in the quinone tautomers of **2** and **8**, peri interactions lead to considerably distorted structures for **2c-H2** and **8-H2**. However, despite these deficiencies, conformational energy differences, summarized in Table S12, can provide at least some crude estimate of intramolecular H-bond strengths for these compounds. It is well-known that the hydrogen-bond strength decreases with increasing solvent dipole moment; for instance, in β-aminoacrolein, a reduction from ca. 5 kcal mol^{-1} in the gas phase to ca. 2−3 kcal mol^{-1} in aqueous solution (PCM, MP2/6-31G**) was found.[7a] Therefore, we have evaluated conformational energy differences also for aqueous, and in some selected cases, acetonitrile solution (PCM, B3LYP/6-311+G**

SCHEME 2: Conformations Used for Estimating the Strength of Intramolecular Hydrogen Bonds



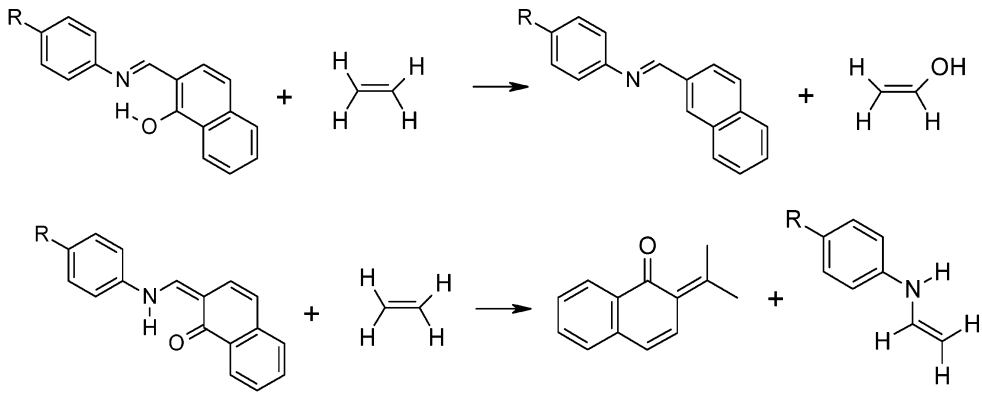
single point calculations, Table S12). Generally, a drop of ca. 4 kcal mol^{-1} (in some cases up to 15 kcal mol^{-1}) for conformational energy differences is obtained by the PCM model. Only for transition states is almost no effect found. Apparently, in TSs the intramolecular hydrogen bond is strong enough to resist being broken by solvent.

3.3. Barriers to Proton Transfer. The importance of the proton transfer (PT) transition state on the strength, electrostatic/covalent nature, and single- vs double-well character of resonance-assisted intramolecular hydrogen bonds in enols of β-dicarbonyl compounds and/or enaminones and related heterodienes, as well as for classification of hydrogen bonds in general, has been stressed recently.[5a,c] Chemical modification results in a splitting of the two competing H-bonds to a higher-energy tautomer with a stronger hydrogen bond, being closer to the PT transition structure, and a more stable tautomer, which is farther from the barrier and, thus, has weaker hydrogen bonding.[5a] Such an inverse relationship between the proton-transfer barrier and the strength of the hydrogen bond has already been established earlier by Scheiner.[29a] Proton-transfer barriers as an index of hydrogen bond strength should be less sensitive to the problems associated with conformer energy differences. From the data given in Table S12, one can deduce gas-phase PT barriers of 1.43, 1.35, 3.76, 0.62, and 0.68 kcal mol^{-1} for the phenol tautomers of compounds **1c**, **2c**, **5c**, **7**, and **8**, respectively, and of 2.30, 1.23, −0.15, 2.56, and 1.74 kcal mol^{-1} for the corresponding quinonoid forms. In the case of the naphthalene derivatives, the phenol (imino enol (**1**) or azo (**7**, **8**)) tautomer has a lower or equal (**2**) barrier (stronger hydrogen bond) than the enaminone (hydrazo) forms in line with the slightly greater stability of the latter tautomeric forms. In contrast, for the salicylidene anil **5** the PT barrier for the quinonoid form essentially vanishes. Not surprisingly, for salicylidene anils, detectable amounts of the enaminone tautomer are present only in highly polar media (see PCM data in Table S12).

3.4. Homodesmotic Reaction. As an alternative to conformational energy differences, homodesmotic reactions have been proposed to assess the strength of intramolecular hydrogen bonding.[39a] Relevant reaction energies (see Scheme 3 for the reactions used) are summarized in Table S13. For enol imine (azo) tautomers of para derivatives (**4**, **6**, and **9**) the analogous homodesmotic reaction energies are quite small (<0.1 kcal mol^{-1}), indicating that, essentially, pure hydrogen-bonding energies are described thereby. For the corresponding enaminone (hydrazone) tautomers, larger reaction energies are obtained (<2.5 kcal mol^{-1} for **4** and **9**; 5.2 kcal mol^{-1} for **6**), making these data less reliable as measures for H-bond strengths. Although the data in Table S13 are corrected for this para effect, hydrogen bonding appears to be overestimated for keto amine (hydrazo) tautomers. Comparison within one tautomeric series (enol imine (azo) or enaminone (hydrazo)), however, should be possible. For both tautomeric species, the azo analogues are predicted to have weaker hydrogen bonds than the corresponding Schiff bases (**8A** vs **2c**−**A**, **8H** vs **2c**−**H**; **7A** vs **1c**−**A**; and **7H** vs **1c**−**H**, Table S13) as also deduced from the experimentally determined solvent effects on K_T. Replacing phenyl by alkyl (**2** vs **10**) results in stronger hydrogen bonding.

3.5. NBO Analysis. Based on a detailed experimental (X-ray crystallography, IR, and NMR spectroscopy), as well as a DFT computational study,[5a−c] an essentially covalent nature for the H-bond in the proton-transfer TS and a more covalent character for the O−H···N than the N−H···O one has been inferred.[5a] Recently, the second-order stabilization energy resulting from charge transfer of the hydrogen acceptor lone pair orbital (lp(X)) toward the antibonding σ^* (Y−H) bond of a Y−H···X hydrogen bond, $E^{(2)}$ (lp(X) → σ^* (Y−H)), as derived from an NBO analysis,[40] has been used for H-bond characterization.[41] In line with the above conclusions, the largest values for $E^{(2)}$ are obtained for TSs ($E^{(2)}$ = 150−250 kcal mol^{-1}), to be

SCHEME 3: Homodesmotic Reactions Used for Estimating the Strength of Intramolecular Hydrogen Bonds



compared to those for O−H···N ($E^{(2)}$ = 30−36 kcal mol^{-1}) and N−H···O ($E^{(2)}$ = 16−21 kcal mol^{-1}) bridges. However, no clear three-center bonds were detected by the NBO analysis.

Conclusion and Outlook

Imino enol ⇄ keto amine tautomerization constants K_T and thermodynamic parameters ΔH_T and ΔS_T for 1-hydroxy-2-naphthaldehyde Schiff bases **1a**−**e** have been determined by a chemometric analysis of the respective UV/vis spectra. Both donor and acceptor substituents in the para position of the *N*-aryl moiety decrease K_T. Polar solvents shift the equilibria toward the quinone tautomer. Ab initio (HF, MP2) and density functional theory (B3LYP) calculations are used to rationalize the experimental findings. Among the computational procedures, B3LYP calculations yield the best agreement with experimental ΔH_T values. Hartree−Fock and, especially, MP2 overestimate the stability of the phenol tautomers. Comparison is made with Schiff bases of the positional isomers 2-hydroxy-1-naphthaldehyde **2a**−**e**, 3-hydroxy-2-naphthaldehyde **3**, and 4-hydroxy-1-naphthaldehyde **4,** as well as the corresponding azo analogues **7**−**9**. Replacing the *N*-aryl group by *N*-alkyl (**2** vs **10**) strongly decreases K_T. Intramolecular hydrogen bonding is characterized by geometric (r(N···O)) and energetic (conformer energies, homodesmotic reactions, proton-transfer barriers) criteria. In line with conclusions drawn from linear solvation energy relationships, the intramolecular hydrogen bond in azo analogues is found to be weaker than in the corresponding Schiff bases. The importance of intramolecular hydrogen bonds on the tautomeric equilibria is indicated by a clear correlation between K_T and the differences between r(N···O) of the respective enaminone (hydrazo) and imino enol (azo) tautomers. Solvent effects on substituted derivatives of salicylidene anils **5a**−**e**, as well as on **1c**, can be quite successfully described by the polarizable continuum model (PCM) or the Poisson−Boltzmann SCRF (PB-SCRF) procedure. In contrast, solvent effects on the substituted derivatives of **1** and **2** are rather poorly described by either solvation model. This drawback needs further scrutiny, possibly by inclusion of explicit solvent molecules in the calculations. Investigations along these lines are in progress.

Experimental Section

Synthesis and Determination of K_T. Compounds **1a**−**e** have been synthesized by a conventional condensation method and then purified by multiple recrystallizations to constant melting point and, if needed, by column chromatography. The purity has been checked by GC/MS.

The solvents used (listed in Table 7) were of spectral or extra pure grade. The absorption spectra at room temperatures were recorded on a Varian Carry 50Bio UV/vis spectrophotometer. The low-temperature spectra (100−300 K) were recorded on a home-built spectrophotometer using a specially constructed 6 mm thick cell cooled by a Cryodyne (CTI Cryogenics) model 21 closed-cycle helium cryostat. An ordinary deuterium lamp was used as light source, the signal was detected by a PC2000 Miniature Fiber Optic Spectrometer (Ocean Optics, Inc.) and initially processed by OOIBase 32 (Ocean Optics, Inc.) software. The temperature was measured with 2−3K precision. At each temperature, reference spectra of the solvent were recorded. EtOH and methylcyclohexane/toluene 1:1 were used as solvents because they form a transparent glass upon cooling. All spectra were corrected for solvent contraction and processed as described in the literature.[18d]

The molar fractions of the individual tautomers and their spectra were estimated using an advanced chemometric approach for processing UV/vis spectra.[18a,b]

Computational Details. Geometries of all structures were completely optimized for the gas phase using ab initio (HF, MP2[42]) and density functional (B3LYP[43]) methods. Thermodynamic quantities (ΔH and ΔG corrections) were calculated by the standard rigid rotor−harmonic oscillator approximation and are unscaled. Effects of a variety of solvents of different polarity were estimated by single point calculations on the gas-phase geometry using several variants of the polarizable continuum model[36a] (PCM,[36b,c] IEF-PCM,[36d] CPCM,[36e] and SCIPCM[36f]) and the Poisson−Boltzmann (PB-SCRF)[37] model. For some selected compounds, optimization with inclusion of solvent effects (IEF-PCM) was also done. The programs used were Jaguar[44] and Gaussian 98.[45]

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Supporting Information Available: Tables for solvent dependence of K_T of **1c** (Table S1), LSER correlations (S2), total (S3−S5) and relative energies (S6−S7), PCM results for **5** (S8) and **1** (S9), N···O distances (S10), solvent effect on r(N···O) and vibrational frequencies (S11), conformational energies (S12), and homodesmotic reaction energies (Table S13). This material is available free of charge via the Internet at http://pubs.acs.org.

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